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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,845	06/27/2001	Xavier Paliard	1681.002	3705

7590 10/18/2005

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,845	PALIARD, XAVIER	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,10-12,15-21 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,10-12,15-21 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 8/1/05. The amendment filed 8/1/05 is acknowledged. The amendment has been entered. Claims 1-3, 6, 7, 10-12, 15-21 and 41 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 6, 7, 10-12, 15-19 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorzinski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), and further in view of Wakita et al. (JBC, 1998, cited by Applicant).

Gorzinski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorzinski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorzinski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that sustained expression of specific HCV genes in the liver of an animal can produce immunological tolerance to the HCV gene (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene (i.e., HCV E1 or HCV E2) can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings based on the teaching of Wakita that an animal having sustained expression of HCV E1 or HCV

E2 in the liver of an animal results in an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita). Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Claims 1-3, 6, 7, 10-12, 15-21 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorzinski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), further in view of Wakita et al. (JBC, 1998, cited by Applicant) and further in view WO 97/47358 (Donnelly et al.).

As indicated above, Gorzinski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorzinski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorzinski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that sustained expression of specific HCV genes in the

liver of an animal can produce immunological tolerance to the HCV gene (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice), and the HCV NS5a gene was recognized in the prior art as an HCV gene which could be used to raise an immunological response to HCV in an animal (e.g., see Donnelly et al.).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Donnelly specifically teaches a nucleic acid encoding the HCV NS5a gene (e.g., see Figure 12) which can be used to raise an immunological response to HCV in animal (e.g., see page 1, lines 16-21; page 3, lines 17-31; page 10, line 31 through page 1 line 35; page 20, lines 14-17; claims 1, 2, 15; etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to the HCV NS5a gene can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings and make the HCV NS5a tolerant animal based on the teaching of Wakita that an animal having

sustained expression of an HCV gene in the liver of an animal results in an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita), and further in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic HCV gene. Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Response to Arguments

Applicant's arguments filed 8/1/2005 have been fully considered.

With respect to the rejection of claims under 35 USC 102(b), the rejections have been withdrawn in view of the amendment which enters the limitation that the immunogen is a hepatitis C virus (HCV) immunogen (previously in claims 4 and 5 which were not rejected under 102(b)).

With respect to the rejection of claims under 35 USC 103, Applicants argue that it is well settled that prima facie obviousness can only be established if the following three basic criteria are met: (1) there must be some suggestion or motivation to modify the reference; (2) there must be a reasonable expectation of success (for the modification and/or combination; and (3) the prior art references) must teach or suggest all the claim limitations as indicated in MPEP 2143. Further, Applicants submit that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. In re Vaeck, 20 USPQZd 1438 (Fed. Cir. 1991). Applicants contend that the Office has not satisfied these criteria.

Specifically, Applicants assert that Gorzinski did not deliver DNA or an immunogenic protein to an animal; Nakai, Wakita and Donnelly do not provide the missing link; none of the cited art, either alone or in combination teaches or suggests methods and as claimed; and that the rejection was made using hindsight reconstruction of the instant rejection (see pages 8-11 of the response filed 8/1/2005).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the references are reasonably pertinent to the particular problem with which the applicant was concerned. Specifically, Gorzinski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal, Nakai teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal, Wakita teaches that sustained expression of specific HCV genes in the liver of an animal can produce immunological tolerance to the HCV gene, and Donnelly teaches that the HCV NS5a gene was recognized in the prior art as an HCV gene

which could be used to raise an immunological response to HCV in an animal. Therefore, all of the references are pertinent to the instant invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Wakita that an animal having sustained expression of an HCV gene in the liver of an animal results in an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" provides the motivation for combining the references. Furthermore, one of ordinary skill in the art would have the knowledge to recognize that portal injection of a vector that expresses a protein is a convenient way of producing an animal that expresses a foreign gene, thus providing further suggestion and motivation to combine the references.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Therefore, Applicants arguments are not persuasive and the rejection set forth herein is appropriate.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER